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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,532	01/25/2002	Jeffrey A. Lyon	003/240/SAP	2344

7590 10/01/2004

ATTN: MCMR-JA (Ms. Elizabeth Arwine-PATENT ATTY)
U. S. Army Medical Research and Materiel Command
504 Scott Street
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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,532	LYON ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

1. The after final response filed on 8/26/04 has been entered into the record. Upon further consideration and review of the application, the final rejection as set forth in the previous office action is hereby withdrawn.

Status of Claims

2. Claims 1, 3 and 5 have been amended.

Claims 2, 4 and 6 are cancelled.

Claims 1, 3, 5 and 7-11 are pending and are under examination in the application.

Specification Informalities withdrawn

3. In view of amendment and submission of Statement regarding ATCC depository information for plasmid pETATpfMSP-1_{42} (3D7), the Specification Informalities are withdrawn.

Claim Rejections - 35 USC 112, first paragraph withdrawn

4. In view of one the submission of statement (letter 8/4/04 of inventor, E. Angov)) regarding ATCC depository information on plasmid pETATpfMSP-1_{42} (3D7) and attorney of record, Mrs. Ann Hobb's signed statement on page 9, 2nd paragraph of the amendment under Remarks section, filed on 8/4/04 confirming that upon the granting of a patent, the deposit will be freely available to the public without restrictions and that the deposit will be maintained for the required period of not less than 30 years or 5 years beyond the date of the last request for a sample was made, the rejection of claims under 35 U.S.C. 112, first paragraph is withdrawn.

Claim Objection withdrawn

5. In view of amendment to claims 3 and 5, the objection is withdrawn.

Claim Rejections - 35 U.S. C. § 112, second paragraph withdrawn

6. In view of amendment to the claims 1, 3 and 5, the rejection under 35U.S.C. 112, second paragraph is withdrawn.

Claim Rejection - 35 USC § 103 withdrawn

7. In view of amendment to the claims1, 3 and 5, the rejection of claims 1, 3, and 5-11 under 35 U.S.C. 103(a) as being unpatentable over Kumar et al 1995, Molecular Medicine 1, 325-332 or Chang et al 1996, Infection and Immunity 64: 253-261 in view of Genton et al 2000, vaccine 18: 2504-2511 is withdrawn as the prior art does not suggest or teach merozoite surface protein *Plasmodium falciparum* 3D7 as represented by SEQ.ID.NO: 2.

Claim Rejections - 35 USC 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, and 5,7-11 are rejected under 35 USC 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

Claim 1 is drawn to a vaccine comprising a C-terminal 42kD fragment of merozoite surface protein, $MSP\text{-}1_{42}$, SEQ.ID.NO: 2 from *Plasmodium falciparum* 3D7 and an adjuvant selected from the group consisting of A, B, C, D and E. Claims 5-11 are drawn to a method of

inducing protective immune response to malaria comprising administering a composition comprising *P. falciparum* 3D7,MSP-1_{42} SEQ.ID.NO: 2 and an adjuvant selected from the group consisting of A, B, C, D and E.

The specification lacks enabling disclosure for a vaccine or for a method of inducing protective immune response comprising administering a composition comprising a C-terminal 42kD fragment of merozoite surface protein, MSP-1_{42}, SEQ.ID.NO: 2 from *Plasmodium falciparum* 3D7 and an adjuvant selected from the group consisting of A, B, C, D and E that would protect a mammal against malaria infection caused by the *Plasmodium falciparum* for the following reasons:

The specification discloses the isolation and purification of the protein from *P. falciparum* 3D7, SEQ.ID.NO: 2. The specification also teaches on page 59(example 2) the potency of the claimed composition (candidate vaccine) by immunizing mice with the claimed composition. Mice were seroconverted indicating that it is an immunogenic composition. Further, safety and immunogenicity of the product was assessed by biochemical and hematological laboratory tests in rhesus monkeys immunized up to five times and no adverse local responses were observed and all tests were normal. On page 64, immunological studies in animals indicated that the composition used induced a specific antibody response as measured by ELISA (Table 4A) and IFA (Table 4B). The composition also induced cellular Immunity as measured by different cytokine response profiles (Table 5). However, the specification fails to disclose

(1) Animals immunized with claimed immunogenic composition are able to inhibit malaria infection upon challenge either with homologous or heterologous *Plasmodium falciparum.*

(2) The specification lacks correlation between *in vitro* results and *in vivo* results. The specification does not show that the anti- MSP-1_{42} antibodies were protective against malaria infection. Page 64, immunological studies in animals indicated that the composition used

induced a specific antibody response as measured by ELISA (Table 4A) and IFA (Table 4B). However, the specification fails to provide positive correlation between the ELISA titer, the IFA titer and protection, which suggests that MSP-1_{42} might serve as good candidate vaccine.

The state of the art with respect to effective vaccine against *P.falciparum* is at developmental stage in identifying an effective antigen with respect to erythrocytic stage that could be used as a candidate vaccine. Egan et al (Infection and Immunity 1995, 63: 456-466) while testing MSP-1_{19} candidate vaccine antigen state (page 462, right column) " antibodies that recognize epitopes within the Pf MSP-1_{42} and PfMSP-1_{19} (processing products of PfMSP-1) may be involved in protective immunity in malaria" because human sera can inhibit the binding of monoclonal antibodies whose epitopes map to either EGF motif or Mabs, which recognize the double motif structure. However, none of the Mab could inhibit binding of human antibodies. Thus human sera recognize a number of epitopes within MSP-1_{19}". Therefore, induction of malaria-specific antibodies that recognize critical epitopes on MSP-1 is important. While testing synthetic malaria peptide vaccine with various adjuvants Kashala state (Vaccine, 2002,20; 2263-2277,page 2276, first column), "Knowledge of protective immunity in malaria is still incomplete. It is generally believed that induction of malaria-specific antibodies is critical, but perhaps not sufficient for an effective control of human malarial infections perhaps not sufficient for an effective control of human malarial infections". Further, when developing a multiantigen, multistage vaccine candidate, Tine et al 1996 (Infection and Immunity 1996, 64: 3833-3844) state " although in vitro assays of immune function do exist, none correlate with protection". Further, Angov et al (Molecular and Biochemical Parasitology 2003, 128; 195-204) showed that the antibody obtained from rabbits immunized with a composition comprising FMPI (vaccine candidate antigen 3D7, MSP-1_{42}) inhibited 3D7 parasite invasion less efficiently than the FVO strain (see Table 2) in *in vitro* inhibition assays. Further, inhibition of P.falciparum 3D7 invasion

appears to depend on multiplication rate of invasion cycle of the parasite as rate of invasion appears to be faster in strain 3D7 than FVO. Therefore, it suggests that the recombinant protein has not, as yet, been shown to generate protective antibodies, which would be expected of a vaccine against *P.falciparum*. Thus, it is apparent identification of a protective erythrocytic candidate vaccine against P.falciparum is yet to be identified.

In addition, the specification (page 23) defines vaccine as an immunogenic composition capable of eliciting protection against malaria, whether partial or çomplete. A vaccine may also be useful for treatment of an infected individual, in which case ii is called a therapeutic vaccine. The term therapeutic refers to a composition that is capable of treating malaria infection. Similarly, the medical Dictionary defines Pharmaceutical composition as "relating to pharmacy or to pharmaceutics"; "pharmacy" as "the practice of preparing and dispensing drugs", and "drug" as "Therapeutic agent; any substance, other than food, used in the prevention, alleviation, treatment, or cure of disease". While the definition of "pharmaceutical" is broad, it is not so broad to cover **any** use of a substance on or in the body of a subject, only those uses intended to prevent, alleviate, treat, or cure a disease within the animal to which the substance was administered.

In view of these definitions, in the instant application, the animal to which the claimed immunogenic composition is administered is merely being used as a bioreactor to make the antibodies. However, the instant specification does not teach how to use the claimed composition as a vaccine/pharmaceutical composition without undue experimentation, for the prevention, alleviation, treatment, or cure of a disease in the animal to which the substance is administered as defined by the specification.

Thus considering the state of the art in inhibiting malaria as indicated above, in view of definition of vaccine/pharmaceutical composition provided by the instant specification as well as

by medical dictionary, the specification fails to provide sufficient evidence whether the claimed vaccine composition partially or completely inhibited the malaria infection upon challenge. Therefore, the skilled artisan would not be able to use such broadly claimed vaccine/ pharmaceutical composition or using said composition in a method for inducing protective immune response, in view of the unpredictability of the art in inhibiting different strains of *P.falciparum,* the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as broadly claimed.

Claim Rejections - 35 U.S. C. § 112, second paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 1, 3 and 5,7-11 are rejected under 35 U.5.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3 and 5 are vague in the recitation of "A, B, C, D and E " because it is not clear adjuvant source, structure or function of the adjuvant as claimed. Further, the abbreviation "A, B, C, D and E " is used without definition upon their first appearance in the claim. The recitation of the term "A, B, C, D and E " appears to be a lab designation. Since this is merely a lab designation, such terminology change from lab to lab or the same designation can be used for totally different product, other identifying characteristics of the adjuvant must be recited.

Remarks

12. No claims are allowed.

Conclusion

13. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padma Baskar

9/23/04